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## **REMARKS**

Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Claim 30 has been amended. Support for the amendment can be found throughout the specification, including page 22, line 15 to page 23, line 12; Figure 4; and page 97, line 14 to page 98, line 7. Claim 43 has been amended and the support for the amendment is found throughout the specification. Claim 48 was also amended to correct an obvious typographical error.

Claims 50-55 have been added. Applicants submit the newly presented claims are supported throughout the specification including at page 11, line 3; page 13, line 27; page 13, lines 3-27; and page 22, line 15 to page 23, line 12; and page 97, line 10 to page 98, line 4.

Therefore, claims 30-55 are pending in the application.

## **Objections**

### **Specification**

The Examiner maintains the objection to the specification because the newly provided pages of the tables have margins that are still too small to accommodate the hole punching. Applicants submit herein replacement tables 6.1-6.15 having a larger top margin. Withdrawal of the objection is requested.

### **Claim Objections**

Claim 48 was objected to for a typographical error where "C<sub>H</sub>3 domain" is incorrectly set forth as "C,3 domain." Claim 48 as amended corrects this error. Withdrawal of the objection is requested.

### **Claim Objections/Rejection Withdrawn**

Applicants acknowledge the withdrawal of the objection to the declaration. Applicants acknowledge the withdrawal of the rejection of claims 30-49 under 35 U.S.C. § 112, second paragraph. Applicants acknowledge the withdrawal of the 35 U.S.C. § 102(b) rejection of claims 30-32, 37, 40 and 42 in view of Carter. Applicants further acknowledge the withdrawal of the rejection of claims 30, 31, 37, 40, 41 and 42 under 35 U.S.C. § 102(b) in view of Tso. Applicants acknowledge the withdrawal of the 35 U.S.C. § 102(e) rejection of claims 30-42 in

view of Carter. Applicants also acknowledge the withdrawal of the rejection of claims 30-49 under 35 U.S.C. § 103(a) in view of Vaughan, Bosslet and the Carter references.

### **35 U.S.C. 112, first paragraph**

#### **Enablement**

Claims 30-42 stand rejected under 35 U.S.C. 112, first paragraph, for an alleged lack of enablement. The Examiner contends that the specification fails to teach how to make bispecific antibodies where the light chain is identical. The Examiner also contends that the specification fails to teach that altering the light chain will still allow for a bispecific antibody that can bind to antigen. The Examiner asserts that changes in antibody binding domain especially in CDRs may result in a loss of affinity. Applicants respectfully traverse this rejection.

Applicants contend that one of skill in the art reading the specification would be able to make the multispecific antibodies as claimed by Applicants without undue experimentation. There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quantity of experimentation. MPEP 2164.01(a) citing *In Re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Only a reasonable correlation between the specification and the scope of enablement is required.

Applicants submit that they have described how to make the claimed multispecific antibodies. Applicants have described in detail the preparation of polypeptides with multimerization domains at pages 47-56, and expression of heteromultimers having common light chains at pages 56, line 11, to page 72, line 15. The Examples provided detailed instructions for forming multimerization domains (Examples 1, 2 and 3) and identification of light chain sequences that have at least 98% and up to 100% sequence identity (Example 4, Table 6). Several pairwise comparison of antibodies with different specificities were made and a number of common light chains were found as described at pages 96, line 20, to page 97, line 10. Moreover, alignments of light chain sequences having at least 98% sequence identity were described and exemplified at page 97, line 10, to page 98, line 3. Applicants have described how to select light chains that are identical and/or to alter light chains that have at least 98% sequence identity. (See figure 4 and pages 97-98) The Examiner's attention is drawn to Example 4, Section

C, where Applicants exemplify the construction, purification, and characterization of an anti-Ob-R/Anti-HER3 antibody of the invention. Therefore, Applicants submit the disclosure exemplifies the generation of an antibody having light chains that have at least 98% or even 100% sequence identity. Applicants also contend that they have taught how to alter or select the light chain so that it can retain antigen binding.

Applicants respectfully submit that the Rudikoff reference concerning the unpredictability of antibody engineering is not relevant for evaluating enablement of this application, because Rudikoff was published in 1982, a full 15 years before the May 1997 priority date of the present application. Applicants submit that during the intervening period, the level of knowledge and predictability in the art of antibody engineering has increased considerably, such that one of skill in the art at the time of filing would readily be able to make and use the claimed invention.

Applicants submit that the level of skill and knowledge in the art regarding antibody structure is now well developed. Several molecular modeling programs can be used to predict and identify which amino acid positions can be varied in antibody structure. In addition, the considerable past and present success in the field of antibody engineering involving the humanization of antibodies clearly shows that CDR regions can be imported from one species into the framework region of another species that may greatly differ in amino acid sequence, and yet still maintain antibody specificity. Therefore, Applicants submit that it is well known in the art that antibody variable domains can be significantly modified and still maintain structure and function.

Furthermore, Applicants have provided guidance in how to determine which amino acid sequences may be varied to form a common light chain that nevertheless maintains the ability to bind to the heavy chain, and form binding domains still capable of binding antigen. The Examiner's attention is called to Example 4 and Figure 4. Here, Applicants have directed one of skill in the art to align the light chain variable domain sequences of paired light chains having at least 98% sequence identity, and then to identify those amino acid residues that differ and could be altered. In Figure 4, Applicants have explicitly described the alignment of antibody variable light chain sequences, and have identified amino acid positions that differ, and could be altered yet still maintain antigen binding activity.

As stated above, the present application discloses several light chains suitable for use in the present invention whose amino acid sequence identities are not identical. See Appendix/Table 6, Figure 4, and Figure 8. Applicants have also described a method for identifying light chain sequences that have at least 98% sequence identity between antibodies of different specificities. (See, for example, Example 4, page 96, line 1 to page 98, line 7). These light chains are from antibodies that are selected for binding to the specific antigen. The selected light chains are already known to bind the antigen. Applicants further disclose that in some embodiments, the light chains were aligned and the amino acid residues that differ between the sequences were identified and could be altered (page 97, lines 27-30). Furthermore, Applicants have disclosed a method of testing the binding specificity of the antibodies of the invention (page 101, line 19 to page 102, lines 15).

Applicants submit it would be routine experimentation for one of skill in the art using the methods as described in the invention to determine if the bispecific antibody with a first or second light chain having at least 98% sequence identity would bind to both of the antigens, or to retain the ability to pair with either heavy chain. The need for routine experimentation to practice Applicants' invention as claimed does not render the claims nonenabled. Indeed, the fact that even complex experimentation must occur to make and use the disclosed invention does not necessarily make it undue, if the art typically engages in such experimentation. MPEP 2164.01.

For at least the foregoing reasons, Applicants respectfully submit that the present disclosure provides substantial guidance in making and using the full scope of the claimed invention. Applicants therefore respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph rejection.

#### **Written Description**

Claims 30-42 stand rejected under 35 U.S.C. 112, first paragraph, because the disclosure allegedly fails to describe the claimed genus of compounds. The Examiner contends that the specification only provides examples of bispecific antibodies where the light chains are identical, such that claims to light chains that are not identical are not supported and represent new matter.

The fundamental factual inquiry in whether the claims are sufficiently described "is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP 2163

I.B. The specification need not describe *ipsis verbis* what is recited in the claims; rather, the claim limitations may be supported in the specification through express, implicit, or inherent disclosure. *Id.* Furthermore, Applicants need not disclose in detail what is conventional or well known to one of ordinary skill in the art. MPEP II 3(a). "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." *Id.*

Claims 30-42 recite methods of preparing multispecific antibodies comprising a first polypeptide and at least one additional polypeptide, wherein the light chains of the first and additional polypeptides each have three CDR regions, have at least 98% sequence identity, and only differ from one another at amino acid positions outside of the CDR regions. Applicants submit that one of skill in the art at the time of filing would have clearly understood from reading the specification that Applicants were in possession of these claimed methods at the time of filing.

Applicants' invention is directed to methods of generating multispecific antibodies comprising binding domains for more than one antigen. Applicants have explicitly disclosed that paired light chains having at least 98% sequence identity can very likely be found for any V<sub>L</sub> comparison (page 97, lines 6-9). Applicants have disclosed the panning of a large human scFv antibody library for antibodies specific for eleven different antigens that represent considerable variation in structure and function (page 95, line 27 through page 96 line 9). After comparing the V<sub>L</sub> sequences of the antibodies, Applicants discovered at least one, and often more than one, light chains having at least 98 % sequence identity for most pair wise comparisons (page 96, line 21 through page 97, line 26, Table 6, Appendix, Figure 4 and Figure 8). Based upon these results, it is likely that light chains that have at least 98% sequence identity can be found for any V<sub>L</sub> comparison. In fact, the majority of pairwise comparisons identified light chains having at least 98% sequence identity. These light chains were selected for binding to the specific antigen and, thus, could bind to the specific antigen of choice.

Applicants have also shown that aligning the identified light chain sequences shows where changes outside of the CDR regions can be made. Indeed, Applicants disclose that light chains having 98-99% sequence identity with the light chain of a prospective scFv can even be substituted with the paired light chain in an antibody and retain binding specificity (page 97, line

30 through page 98, line 33). One of skill in the art would readily apprehend that the specification discloses that light chains having at least 98% identity are suitable for use in the formation of a multispecific antibody.

Therefore, Applicants submit that one of skill in the art at the time of filing would readily recognize that Applicants were in possession of methods of preparing multispecific antibodies comprising a first polypeptide and at least one additional polypeptide, wherein the light chains of the first and additional polypeptides have at least 98% sequence identity.

The Examiner contends, however, that the claimed antibodies are not adequately described in the specification because the specification does not provide working examples of antibodies having light chains that are not identical. Applicants respectfully disagree that working examples are required.

Applicants respectfully submit that, for purposes of determining the adequacy of written description, the patent laws do not require Applicants to provide working examples representative of the full scope of the invention. A working example is merely one manner in which Applicants may show possession of an invention. MPEP 2163 II.A 3(a). As stated above, the fundamental, relevant inquiry is whether the specification conveys with reasonable clarity to one of skill in the art that Applicants were in possession of the claimed invention.

Since Applicants disclose light chains having at least 98% sequence identity and in some embodiments, whose amino acid residues vary outside of their CDRs, and teach that such light chains may be substituted for each other and retain binding specificity in a multispecific antibody, Applicants were clearly in possession of the invention as claimed at the time of filing. Applicants submit that working examples are not required by the written description guidelines, and that, furthermore, Applicants need not disclose in *ipsis verbis* every limitation of the claims. Applicants respectfully submit that claims 30-42 are amply described in the specification for at least the foregoing reasons. Furthermore, since the claims as amended are fully described by the specification, Applicants submit that no new matter was added by the amendments. Withdrawal of the rejection is requested.

### **35 U.S.C. § 103**

Claims 43-49 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Ridgway, Carter (U.S. Pat. No. 5,807,706), or Carter (WO 96/27011), in view of Kostelney and further in

view of Vaughan. The Examiner contends that Ridgway, Carter (U.S.) or Carter (WO) teach methods of engineering multimerization domains onto polypeptides for making bispecific antibodies. The Examiner further asserts that Kostelney teaches a method of making bispecific antibodies, and teaches a method for improved heterodimerization using leucine zippers. The Examiner further states that Kostelney teaches that unwanted proteins may still be formed because of mismatching of different L chains and H chains. The Examiner then contends that Vaughn teaches examples of scFvs where identical light chains are paired with two different heavy chains to bind to two different antigens. The Examiner concludes it would be obvious to alter the methods of Ridgway, Carter (U.S.) or Carter (WO) to include finding a light chain that could be used for each of the binding domains. The Examiner asserts that one of skill in the art would be motivated to use the methods of Vaughn to find such chains because of the problem taught by Kostelney that unwanted antibody products may be formed due to mismatching of light and heavy chains. Applicants respectfully traverse this rejection.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) suggestion or motivation to, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, modify the reference or combine the reference teachings; and 3) a reasonable expectation of success. MPEP 706.02(j). Applicants submit that not all of these requirements have been met, at least because there is no motivation or suggestion to combine the references in the manner asserted by the Examiner, and because there would be no reasonable expectation of success in doing so.

As an initial matter, Applicants submit that the Carter U.S. reference (U.S. Pat. No. 5,807,706) is not prior art under 35 U.S.C. 103(c). The instant application is a continuation application of U.S. Application Ser. No. 08/850,058, filed on May 2, 1997. The Carter reference is a U.S. patent with a filing date of May 3, 1995 and an issue date of September 15, 1998. Therefore, this references qualifies as prior art only under 102(e).

A reference that is prior art only under 102(e) cannot be used, under 103(c), in an obviousness rejection if the subject matter of the cited reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.



Applicants hereby make a clear statement of entitlement to exclude the Carter patent as prior art. The Carter patent is assigned to the assignee of the present application. It, and the present application were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

**1) The Examiner has not established a proper motivation to combine these references.**

To establish a prima facie case of obviousness, there must be some suggestion or motivation to combine the reference teachings. MPEP 2142. The Examiner bears the initial burden "to provide some suggestion of the desirability of doing what the inventor has done." *Id.* Applicants respectfully submit that no such motivation exists in the cited references, or in the knowledge of the art, to do what the present inventors have done, namely, selecting a common light chain for each polypeptide of the claimed multispecific antibody.

The Carter reference (WO 96/27011) and the Ridgeway reference are each directed to forming heteromultimers with a multimerization region. These references do not teach or suggest a preparing a heteromultimer by selecting a light chain that associates with the binding region of each first and additional polypeptide of the multispecific antibody. Indeed, the Ridgeway reference is directed to an antibody/immunoadhesin bispecific molecule, and a first and second light chain are not even found in this type of molecule. The Carter reference is directed to forming a multimerization domain, and is silent regarding the selection of a light chain.

Nor does the Kostelney reference remedy this deficiency. This reference is directed to the use of leucine zipper domains to increase the yield of correctly paired bispecific F(ab')<sub>2</sub> heterodimers. The Examiner asserts, however, that this reference provides the motivation to look for a single light chain that binds to two different heavy chains as taught by Vaughn, because this reference allegedly teaches that unwanted proteins may be formed from mismatching of different L chains and H chains.

Applicants respectfully submit that the Examiner has mischaracterized the Kostelney reference. In the method of Kostelney, two heterodimer-forming zipper peptides derived from the Fos and Jun proteins were respectively linked to the Fab' portions of two different mAb (145-2C11 and anti-Tac) by gene fusion (See Abstract). The anti-Tac Fab'-Jun and anti-CD3 Fab'-Fos

were then expressed individually as homodimers, reduced *in vitro* to form monomers, and then mixed and reoxidized together to form bispecific antibody products (*Id.*, and page 1548, fourth full paragraph).

Kostelney teach that the two proteins are mixed *in vitro* to form the bispecific antibodies, after having been expressed in separate cells. This method is preferred because of the ease of achieving purity during large-scale production of bispecific antibodies, and because "the T cell binding component of the bispecific antibody such as anti-CD3-Fos need only be generated once, since it can then be combined with a variety of Fab'-Jun components to target different cells" (page 1552, first paragraph).

Therefore, in this method, there is no opportunity for mismatching of light chains to occur. Each mAb-Fab' is individually expressed such that only the cognate light chain is available to associate with the respective Fab'. Consequently, the method of Kostelney does not have the problem of mismatched H and L chains in the final antibody product. Applicants respectfully submit that the Examiner's citations to Kostelney regarding the problem of mismatched chains relate only to a method of forming the antibody that is not the preferred method of the reference. Kostelney states that if the antibody is formed from the two Fab' proteins *in vivo* rather than *in vitro*, mismatching of H and L chains can occur (page 1551, last paragraph to page 1552, first full paragraph). Furthermore, Kostelney states that using *in vivo* methods, "it is difficult to express the two Fab' zipper proteins at equal levels in one cell line, and the excess proteins may form homodimers." , implying that this method is not preferred.

Therefore, Kostelney directs one of skill in the art away from using the *in vivo* method, where each antibody is produced in the same cell, which may lead to mispairing of H and L chains and formation of homodimers. Rather, Kostelney provide a method that eliminates the problem posed by such mismatching of chains. Furthermore, Kostelney does not teach or suggest that a method comprising selecting a common light chain be employed to address the problem of mispairing of the light chains. Consequently, one of skill in the art would not be motivated by Kostelney to seek other solutions to the problem, because Kostelney provides a solution to the problem and directs one of skill in the art away from a method where both polypeptide chains are expressed in the same cell.

The deficiencies of Kostelney are not remedied by reference to Vaughn. The Vaughn et al. reference is directed to preparing a scFv phage library of naïve antibody variable domains.

The reference describes the construction of a large repertoire of single chain Fvs derived from functional V genes. This reference describes that the same light chain was sometimes found to pair with different heavy chains. This reference nowhere discusses multispecific antibodies, nor does it suggest that identical light chains be selected for use in a multispecific antibody. The reference nowhere teaches or suggests that there is any advantage of selecting identical light chains over any other light chains.

Applicants respectfully submit, therefore, that the Examiner has failed to establish a motivation to combine the references in a manner that teaches or suggests all limitations of the instant claims. Applicants respectfully submit, therefore, that the Examiner is exercising impermissible hindsight, by utilizing the knowledge disclosed in the Applicants' specification to provide the motivation to combine the teachings of Vaughn and Kostelny. MPEP 2145 X. A. Applicants submit, therefore, that claims 43-49 are patentable over the cited references, at least for this reason and respectively, request withdrawal of the rejection.

**2) The Examiner has failed to show that there would be a reasonable expectation of success in obtaining a bispecific antibody having a light chain capable of associating with the binding region of each first and additional polypeptide of the multispecific antibody.**

In order to establish a prima facie case of obviousness, the Examiner must establish a reasonable expectation of success. The suggestion for the claimed invention and a reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. In re Vacek, 20 USPQ2d 1438, 1142 (Fed. Cir. 1991).

Applicants submit that the Examiner has not established a reasonable expectation of success of increasing yields and efficiency of producing multispecific antibodies using the methods as claimed by Applicants. None of the cited references teach or suggest a method comprising selecting a light chain encoding nucleic acid sequence, when the light chain associates with the binding region of the first and additional polypeptide or that such a method could be utilized to produce multispecific antibodies with improved yield.

Carter & Ridgway are silent regarding this issue. The Kostelny et al. reference is directed to forming bispecific antibodies. However, the Kostelny et al. reference directs one of skill in the art to a different method for forming bispecific antibodies wherein antibodies were expressed separately in different cells as homodimers, reduced *in vitro* to form monomers and

then mixed and reoxidized to form the bispecific antibody products. There is no teaching or suggestion in Kostelney that a method where both polypeptides are expressed in the same cells could be utilized to produce a multispecific antibody in high yield. In fact, the reference indicates that such methods may be undesirable.

As discussed previously, Vaughan et al. is not directed to the problem of preparing multispecific antibodies much less preparing multispecific antibodies in high yield. There is no teaching or suggestion in Vaughan et al. that multispecific antibodies with a common light chains can or should be formed. In fact, in Vaughan et al., lack of diversity of the library was viewed as a negative aspect of the library. In addition, Vaughan et al. did not teach or suggest that ScFv with light chains having at 100% sequence identity would be found in the majority of possible pairwise combinations of two different antigen specificities.

Thus, based on the teachings of these references one of skill in the art would not have had a reasonable expectation of success of preparing a multispecific antibody comprising a light chain encoding nucleic acid, wherein the light chain associates with the binding region of each first and addition of polypeptide of the multispecific antibody.

Based on the foregoing, Applicants contend the Examiner has not established a prima facie case of obviousness for at least these reasons and request withdrawal of the 35 U.S.C. § 103 rejection.

### **Double Patenting**

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting, as unpatentable over claims 30-51 of copending Application No. 09/863,693. Upon notice of allowable claims in this case, Applicants will timely file a Terminal Disclaimer under 37 C.F.R. 1.321(c) if appropriate to overcome this rejection.

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting, as unpatentable over claims 47-63 of copending Application No. 09/520,130. Upon notice of allowable claims in this case, Applicants will timely file a Terminal Disclaimer under 37 C.F.R. 1.321(c) if appropriate to overcome this rejection.

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting, as unpatentable over claims 1-29 of copending Application No. 10/143,437. Upon notice of allowable claims in this case, Applicants will timely file a Terminal Disclaimer under 37 C.F.R. 1.321(c) if appropriate to overcome this rejection.

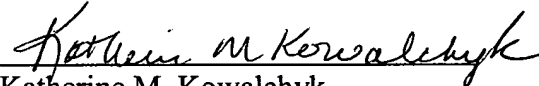
**Summary**

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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Date: May 13, 2004

  
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[illegible]

Table 6.1

[illegible]

[illegible]



ME	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51
24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51
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61	48	61	68	60	73	60	59	59	48	68	50	77	70	49	44	49	49	70	48	49	72	49	66	74	75	70	65
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-	43	48	43	47	45	43	44	44	98	47	80	48	47	94	95	84	83	46	99	99	48	83	43	46	47	45	
-	-	61	99	61	99	88	100	43	72	45	67	59	44	40	44	44	44	62	43	44	61	44	54	59	60	61	
-	-	60	80	60	80	55	59	48	85	49	65	94	48	44	44	46	46	93	48	49	78	46	58	60	60	61	
-	-	60	98	87	99	43	71	45	67	58	44	40	44	44	44	44	44	61	43	44	60	44	53	58	59	60	
-	-	60	57	59	47	79	50	66	84	48	43	46	46	83	47	43	47	43	48	97	46	61	65	66	65	79	
-	-	87	99	45	75	46	67	61	45	41	46	44	61	45	44	44	44	56	43	42	57	42	51	56	57	55	
-	-	88	43	67	44	63	56	43	39	42	40	56	43	42	57	42	51	56	57	58	60	61	62	63	64	65	
-	-	44	74	46	68	60	44	42	45	44	60	44	44	44	44	44	44	44	44	44	44	44	44	44	44	44	
-	-	47	80	48	47	94	95	83	83	46	80	47	48	76	48	80	47	48	76	48	64	62	63	64	65	66	
-	-	50	75	82	47	43	48	48	80	47	48	80	47	48	76	48	80	47	48	76	48	64	62	63	64	65	
-	-	51	50	79	78	81	81	50	80	80	50	80	47	48	76	48	80	47	48	76	48	64	62	63	64	65	
-	-	70	47	46	50	51	69	48	49	65	50	74	72	73	75	64	64	62	63	64	65	66	67	68	69		
-	-	47	43	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	
-	-	91	83	83	47	95	96	49	82	42	46	42	46	47	42	40	42	46	47	42	40	42	46	47	47	45	
-	-	80	81	42	96	98	44	79	99	45	45	46	47	42	40	42	46	47	42	40	42	46	47	47	47	45	
-	-	100	45	84	83	47	99	45	46	47	42	40	42	40	42	46	47	42	40	42	46	47	47	47	47	45	

Table 6.4

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[illegible]

Mask			NpoR			Res																						
52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	
79	80	79	81	81	44	45	45	80	46	46	46	48	72	81	49	46	47	47	45	81	49	81	51	49	44	46	100	
47	47	47	48	50	59	46	45	47	73	73	71	70	42	48	71	69	71	70	70	48	71	47	83	94	59	73	49	
48	48	48	49	51	61	47	46	48	75	75	73	72	43	49	73	71	73	71	72	49	73	48	85	96	61	75	50	
83	84	83	100	81	44	48	46	84	47	47	46	45	88	100	46	43	47	44	45	100	46	99	49	49	44	47	81	
77	78	77	82	79	48	48	47	78	49	49	51	51	80	82	52	48	52	50	50	82	52	82	55	52	48	49	83	
98	99	98	83	76	43	46	44	99	47	47	47	46	73	83	47	43	48	45	46	83	47	82	49	48	43	47	79	
78	79	78	83	80	48	48	46	79	49	49	51	51	74	83	52	48	52	50	50	83	52	82	55	52	48	49	83	
48	48	48	48	49	58	44	44	48	80	80	65	63	41	48	64	60	67	62	64	48	64	47	68	76	58	80	46	
48	48	48	49	51	63	46	48	48	75	75	66	65	42	49	66	61	66	64	65	49	66	48	74	75	63	75	49	
47	47	47	46	49	61	48	47	47	66	66	89	99	41	46	100	95	90	98	88	46	100	45	83	73	61	66	49	
85	85	85	85	81	45	46	46	85	48	48	47	47	77	85	48	45	48	46	46	85	48	85	51	50	45	48	90	
47	47	47	45	47	62	45	46	47	62	62	80	84	40	45	85	84	81	83	79	45	85	44	77	70	62	62	45	
99	100	99	84	77	43	46	44	100	47	47	47	46	74	84	47	43	48	45	46	84	47	83	49	48	43	47	80	
44	44	44	44	46	58	46	45	44	61	61	84	94	40	44	95	90	86	93	86	44	95	43	78	69	58	61	46	
47	47	47	48	50	62	50	49	47	65	65	88	89	42	48	90	86	89	88	88	48	90	47	89	76	62	65	48	
41	42	41	42	44	98	47	46	42	57	58	58	57	38	42	59	52	59	57	57	42	59	42	62	57	98	58	42	
41	42	41	42	44	98	47	46	42	57	58	57	57	38	42	59	52	59	57	57	42	59	42	62	57	98	58	42	
42	43	42	44	46	100	49	48	43	59	60	60	60	40	44	61	54	61	59	59	44	61	43	64	59	100	60	44	
47	47	47	46	49	61	48	47	47	66	66	89	99	41	46	100	95	90	98	88	46	100	45	83	73	61	66	49	
48	48	48	49	51	60	46	45	48	75	75	74	72	71	43	49	72	71	72	70	72	49	72	48	84	95	60	74	50
48	48	48	49	51	61	47	46	48	75	75	73	72	43	49	73	71	73	71	72	49	73	48	85	96	61	75	50	
81	82	81	98	79	43	47	45	82	46	46	45	44	86	98	45	42	46	43	44	98	45	97	48	48	43	46	79	
49	49	49	48	51	61	49	49	49	70	70	89	93	43	48	94	89	90	92	88	48	94	47	83	77	61	70	49	
42	43	42	44	46	100	48	48	43	59	60	60	60	40	44	61	54	61	59	59	44	61	43	64	59	100	60	44	
98	99	98	84	77	43	46	44	99	47	47	47	46	74	84	47	43	48	45	46	84	47	83	49	48	43	47	80	
42	43	42	44	46	100	49	48	43	59	60	60	60	40	44	61	54	61	59	59	44	61	43	64	59	100	60	44	
48	48	48	48	50	61	48	45	48	60	60	74	80	40	46	80	79	75	79	73	46	80	45	71	68	61	60	48	
48	48	48	48	49	51	61	48	45	48	45	58	59	59	40	44	60	53	60	58	58	44	60	43	63	58	99	59	44
42	43	42	44	46	99	49	48	43	58	59	59	59	40	44	60	53	60	58	58	44	60	43	63	58	99	59	44	
47	47	47	46	49	61	48	47	47	66	68	89	99	41	46	100	95	90	98	88	46	100	45	83	73	61	66	49	
44	45	44	46	48	99	48	47	45	59	59	59	59	40	46	60	54	60	58	59	46	60	45	63	58	99	59	46	
42	43	42	42	44	88	48	49	43	57	57	56	56	36	42	57	52	57	55	56	42	57	41	60	57	88	57	44	
43	44	43	45	47	100	47	47	44	58	58	58	58	41	45	59	54	59	57	58	45	59	45	62	57	100	58	46	
98	99	98	83	76	43	46	44	99	47	47	47	46	74	83	47	43	48	45	46	83	47	82	49	48	43	47	79	
47	47	47	48	50	72	48	45	47	63	63	73	78	42	48	79	78	74	77	73	48	79	47	71	68	72	63	50	
79	80	79	81	81	45	46	46	80	47	47	47	47	49	73	81	50	46	48	46	81	50	81	51	50	45	47	100	
48	48	48	50	52	67	47	45	48	73	73	65	65	41	50	66	64	66	64	65	50	66	50	75	74	67	73	51	
47	47	47	46	52	59	46	43	47	64	64	75	83	41	46	84	83	76	82	74	46	84	45	72	70	59	64	49	
94	95	94	83	75	44	47	45	95	47	47	48	47	74	83	48	43	49	46	47	83	48	82	50	49	44	47	79	
95	96	95	80	73	40	43	43	96	43	43	43	42	72	80	43	43	44	43	44	80	43	80	45	44	40	43	78	
83	84	83	100	81	44	48	46	84	47	47	46	45	88	100	46	43	47	44	45	100	46	99	49	49	44	47	81	

Table 6.7

[illegible]

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Table 6.10

46	100	81	84	49	45	83	47	84	47	44	84	47	83	82	46	47	82	81	81	81	82	82	81	47	49	81	83			
63	45	49	48	70	92	46	63	48	64	62	48	64	46	48	80	64	46	49	49	49	46	46	49	64	70	45	46			
46	84	80	86	49	47	100	46	86	47	43	86	47	99	95	45	47	99	80	80	80	98	99	80	47	48	97	100			
47	83	80	86	50	48	100	48	86	48	44	86	48	99	95	47	48	99	80	80	80	98	99	80	48	50	65	72	47	48	
64	47	50	50	75	77	48	61	50	65	61	50	65	48	50	90	65	48	50	50	50	82	82	80	47	49	81	83			
46	99	80	84	49	45	83	46	84	47	44	84	47	83	82	45	47	82	80	80	80	82	82	80	47	49	81	83			
73	45	43	44	68	57	43	68	44	74	54	44	74	43	45	63	74	43	43	43	43	43	43	43	74	66	42	43			
98	46	45	49	80	59	46	75	49	99	59	49	99	46	47	71	99	46	45	45	45	46	46	45	99	74	45	46			
99	47	46	50	80	60	47	76	50	100	60	50	100	47	48	72	100	47	46	46	46	47	47	46	47	46	100	75	46	47	
77	47	47	46	72	60	45	74	46	78	61	46	78	45	47	65	78	45	47	47	47	47	45	45	47	78	70	44	45		
57	44	47	47	66	98	46	58	47	58	57	47	58	46	47	77	58	46	47	47	47	46	46	47	58	65	45	46			
46	83	79	85	49	47	99	46	85	47	42	85	47	98	94	45	47	98	79	79	79	97	98	79	47	48	96	99			
46	84	80	86	49	47	100	46	86	47	43	86	47	99	95	45	47	99	80	80	80	98	99	80	47	48	96	99			
46	83	79	85	49	47	99	46	85	47	42	85	47	98	94	45	47	98	79	79	79	97	98	79	47	48	96	99			
46	100	81	85	49	45	84	46	85	47	44	85	47	84	83	45	47	83	81	81	81	83	83	81	47	49	82	84			
48	81	81	80	52	49	77	46	80	49	46	80	49	77	79	48	49	76	81	81	81	77	77	81	49	51	75	77			
59	44	44	45	65	60	43	61	45	60	100	45	60	43	44	63	60	43	44	44	44	43	43	44	60	61	42	43			
46	48	45	48	49	48	46	44	48	47	49	48	47	46	46	45	47	46	45	45	45	45	45	47	46	45	47	45	46		
45	46	45	46	48	45	44	45	46	46	48	46	48	44	44	45	46	44	45	45	45	45	45	45	46	46	46	43	44		
46	84	80	86	49	47	100	46	86	47	43	86	47	99	95	45	47	99	80	80	80	98	99	80	47	48	97	100			
99	47	46	50	80	60	47	76	50	100	59	50	100	47	48	72	100	47	46	46	46	47	47	46	47	46	100	75	46	47	
99	47	46	50	80	60	47	76	50	100	59	50	100	47	48	72	100	47	46	46	46	47	47	46	47	46	100	75	46	47	
99	47	46	50	80	60	47	76	50	100	60	50	100	47	48	72	100	47	46	46	46	47	47	46	47	46	100	75	46	47	
66	46	46	48	76	73	47	62	48	67	60	48	67	47	48	82	67	47	46	46	46	47	47	46	67	73	46	47			
65	45	48	48	75	79	46	61	48	65	60	48	65	46	48	91	65	46	48	48	48	46	46	46	65	72	45	46			
41	88	72	75	44	40	74	41	75	42	40	75	42	74	73	41	42	74	72	72	72	73	73	81	47	49	82	84			
46	100	81	85	49	45	84	46	85	47	44	85	47	84	83	45	47	83	81	81	81	83	83	81	47	49	82	84			
65	46	49	49	76	80	47	62	49	66	61	49	66	47	49	92	66	47	49	49	49	47	47	47	47	47	47	47	47		
59	43	46	45	72	78	43	58	45	60	54	45	60	43	45	91	60	43	46	46	46	46	46	46	60	71	42	43			
67	47	47	49	76	74	48	62	49	68	61	49	68	48	49	83	68	48	47	47	47	47	47	47	68	73	47	48			
64	44	47	47	74	78	45	60	47	64	59	47	64	45	47	90	64	45	47	47	47	45	45	45	64	71	44	45			
65	45	45	47	75	72	46	62	47	66	59	47	66	46	47	81	66	46	45	45	45	45	45	45	66	72	45	46			
46	100	81	85	49	45	84	46	85	47	44	85	47	84	83	45	47	83	81	81	81	83	83	81	47	49	82	84			
65	46	49	49	76	80	47	62	49	66	61	49	66	47	49	92	66	47	49	49	49	47	47	47	47	47	47	47	47		
45	99	81	84	48	44	83	46	84	46	43	84	46	83	82	44	46	82	81	81	81	82	82	81	67	85	48	49			
66	49	51	51	86	70	49	71	51	67	64	51	67	49	51	77	67	50	51	51	51	49	49	48	48	49	79	96	47	48	
78	49	49	52	90	67	48	72	52	79	59	52	79	48	49	63	60	43	44	44	44	44	44	44	43	43	44	60	61	42	43
59	44	44	45	65	60	43	61	45	60	100	45	60	43	44	63	60	43	44	44	44	44	44	44	43	43	44	60	61	42	43
99	47	46	50	80	60	47	76	50	100	60	50	100	47	48	72	100	47	46	46	46	47	47	46	47	46	100	75	46	47	
45	81	100	85	51	47	80	48	85	46	44	85	46	79	82	48	46	79	100	100	100	79	80	100	46	50	78	80			
46	45	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46	47	71	99	46	45	45	45	45	45	46	46	45	99	74	45	46
46	81	85	49	80	59	46	75	49	99	49	59	49	99	46																



[illegible]



44	46	84	83	83	44	49	46	83	84	41	MpI.16
62	82	48	46	46	62	65	83	49	48	42	MpI.19
43	47	86	100	100	43	46	47	85	86	43	MpI.21
44	48	86	100	100	44	48	48	85	86	44	MpI.24
61	96	50	48	48	61	69	97	51	50	45	MpI.26
44	46	84	83	83	44	48	46	82	84	46	MpI.28
54	61	44	43	43	54	94	61	47	44	47	MpI.29
59	65	49	46	46	59	78	65	50	49	48	MpI.30
60	66	50	47	47	60	79	66	51	50	49	MpI.31
61	65	46	45	45	61	99	65	48	46	50	MpI.32
57	78	47	46	46	57	60	79	49	47	51	MpI.33
42	47	85	99	99	42	46	47	84	85	52	MpI.35
43	47	86	100	100	43	46	47	85	86	53	Musk.01
42	47	85	99	99	42	46	47	84	85	54	Musk.02
44	46	85	84	84	44	48	46	83	85	55	Musk.06
46	49	80	77	77	46	50	49	78	80	56	NpoR.25
100	60	45	43	43	99	61	61	46	45	57	NpoR.44
49	48	48	46	46	49	45	48	49	48	58	NpoR.53
48	47	46	44	44	48	46	47	48	46	59	NpoR.81
43	47	86	100	100	43	46	47	85	86	60	NpoR.86
59	66	50	47	47	59	78	66	51	50	61	Rse.01
60	66	50	47	47	60	79	66	51	50	62	Rse.02
60	88	48	47	47	60	65	89	49	48	63	Rse.03
60	98	48	46	46	60	65	99	49	48	64	Rse.04
40	41	75	74	74	40	44	41	80	75	65	Rse.07
44	46	85	84	84	44	48	46	83	85	66	Rse.08
61	99	49	47	47	61	66	100	50	49	67	Rse.15
54	94	45	43	43	54	62	95	46	45	68	Rse.16
61	90	49	48	48	61	66	90	50	49	69	Rse.18
59	97	47	45	45	59	64	98	48	47	70	Rse.20
59	88	47	46	46	59	65	88	48	47	71	Rse.21
44	46	85	84	84	44	48	46	83	85	72	Rse.22
61	99	49	47	47	61	66	100	50	49	73	Rse.23
43	45	84	83	83	43	48	45	83	84	74	Rse.24
64	82	51	49	49	63	70	83	52	51	75	Rse.52
59	72	52	48	48	59	73	73	53	52	76	Rse.53
100	60	45	43	43	99	61	61	46	45	77	Rse.58
60	66	50	47	47	60	79	66	51	50	78	Rse.60
44	49	85	80	80	44	48	49	85	85	79	Rse.61
59	65	49	46	46	59	78	65	50	49	80	Rse.63
44	46	85	84	84	44	48	46	83	85	81	her3.1
44	49	85	80	80	44	48	49	85	85	82	her3.10

Table 6.14

45	49	100	86	86	45	47	49	99	100	83	her3.11
65	75	53	49	49	64	73	76	54	53	84	her3.12
60	79	48	47	47	60	61	80	49	48	85	her3.16
43	47	86	100	100	43	46	47	85	86	86	her3.18
61	62	47	46	46	60	75	62	49	47	87	her3.19
45	49	100	86	86	45	47	49	99	100	88	her3.22
60	66	50	47	47	60	79	66	51	50	89	her3.3
100	60	45	43	43	99	61	61	46	45	90	her3.4
45	49	100	86	86	45	47	49	99	100	91	her3.7
60	66	50	47	47	60	79	66	51	50	92	obr.1
43	47	87	99	99	43	46	47	86	87	93	obr.11
44	49	85	95	95	44	48	49	83	85	94	obr.12
63	91	49	45	45	63	66	92	51	49	95	obr.14
60	66	50	47	47	60	79	66	51	50	96	obr.15
43	47	85	99	99	43	46	47	84	85	97	obr.16
44	49	85	80	80	44	48	49	85	85	98	obr.17
44	49	85	80	80	44	48	49	85	85	99	obr.18
44	49	85	80	80	44	48	49	85	85	100	obr.19
43	47	85	98	98	43	46	47	83	85	101	obr.2
43	47	86	99	99	43	46	47	85	86	102	obr.20
44	49	85	80	80	44	48	49	85	85	103	obr.21
60	66	50	47	47	60	79	66	51	50	104	obr.22
61	72	52	48	48	60	71	73	53	52	105	obr.23
42	46	85	97	97	42	45	46	83	85	106	obr.24
43	47	86	100	100	43	46	47	85	86	107	obr.26
-	60	45	43	43	99	61	61	46	45	108	obr.3
-	49	47	47	60	66	99	50	49	109	obr.4	
-	-	86	86	45	47	49	99	100	110	veg1.1	
-	-	100	43	46	47	85	86	111	veg1.10		
-	-	-	43	46	47	85	86	112	veg1.2		
-	-	-	-	61	61	46	45	113	veg1.3		
-	-	-	-	66	49	47	114	veg1.4			
-	-	-	-	50	49	115	veg1.5				
-	-	-	-	-	99	116	veg1.6				
-	-	-	-	-	-	117	veg1.8				
108	109	110	111	112	113	114	115	116	117		Clone
					VEGF						

Table 6.15